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The Role of Green Solvents and Catalysts at the Future of Drug Design and of Synthesis

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.71018>

Abstract

Green chemistry is getting extended in many researches and industry areas. Not only pharmaceutical companies but also the other chemical industries started to take a step for green chemistry due to its advantages such as decreasing of waste and cost. With this respect, we have already witnessed that pharmaceutical companies searched out for green protocol when manufactured the pharmaceuticals. Green chemistry strategies can be seen in solvents, catalysts, and the others. So, we have briefly discussed the green solvents and nanocatalysts in this chapter. We hope that this chapter gives a brief consideration of importance of green chemistry.

Keywords: nanocatalyst, pharmaceutical company, green chemistry, environment

1. Introduction

The demand of green chemistry for applying in the pharmaceutical and the other chemical industries is increasingly vital due to the fact that our world faces the environmental challenges of the twenty-first century. US Environmental Protection Agency (EPA) has suggested green chemistry for innovative technologies that reduce toxic, undesired waste, and environmental impact. Green chemistry is thus getting grew as an open light to afford a huge scientific area. After EPA, 12 principles of green chemistry have been gotten more attention and these principles have been considered more seriously by pharmaceutical companies since 1998. Pharmaceutical companies declared that they should improve the environmental performance by utilizing green chemistry. Not only pharmaceutical companies but also the other chemical industries started to take a step for green chemistry due to its advantages such as decreasing of waste and cost. It is assumed that green chemistry can save the industry an

estimated USD 65.5 billion by 2020 [1] primarily by reducing manufacturing costs. If the processes can be implemented right, green chemistry can afford to reduce waste product and decrease the resources consumption. Green chemistry is needed for minimizing of some social risks and safety issues, as well.

In the past decade, some of the large pharmaceutical companies around the world have focused on using green chemistry processes for drug discovery, development, and manufacturing. These firms include Amgen, the Merck Group, Abbott, Eli Lilly, Johnson & Johnson, and Roche [2]. Green chemistry has started to point three lines such as cost, mankind, and our planet. American Chemical Society's Green Chemistry Institute's Pharmaceutical Roundtable was therefore launched and, since 2008, many drug companies have become the members that aim to foster the development of more efficient, less polluting processes. Fortunately, green chemistry celebrates 25 years of progress on 2016 [3].

It can not be denied that people need medicines to cure their diseases some of which are very unpleasant. For that reason, pharmaceutical industry has struggled to have modern synthetic strategies for known and unknown therapeutic reagents. On the other hand, although many successful methodologies were achieved, the toxic properties of many reagents and solvents were not known and the issues of waste minimization and sustainability of solvents and/or unreacted reagents were largely unheard. Chemists and medicinal scientists can reduce the risk to human health and the environment by following all the valuable principles of green chemistry. The most simple and direct way to apply green chemistry in pharmaceuticals is to utilize eco-friendly, nonhazardous, reproducible, and efficient solvents and catalysts in the synthesis of drug molecules, and in researches involving synthetic chemistry.

It has become clear that the chemical and related industries such as pharmaceutical companies are faced with environmental problems. There are a lots of synthetic methodologies and they have generated abundant amounts of waste and chemical industries want to minimize or eliminate this waste. Sheldon has discussed that in the pharmaceutical industries, there is an urgency for consideration of the waste product as a number of by-products produced per kg of product (designated E factor) is about 25 [4]. Innovative strategies on chemistry are the core of the pharmaceutical business. The main point is gathering technology and chemistry to improve lives of patients and minimize environmental impact.

Solvents and stoichiometric reagents are the most important parameters to be considered for greener strategies and these parameters are under investigation in detail by many pharmaceutical companies such as Sanofi-Aventis [5, 6] and GlaxoSmithKline [7]. These companies have suggested that conventional solvents such as halogenated, petroleum-based should be converted into greener solvents such as glycerol, ethyl lactate [8], and water [9]. A catalyst is an another crucial parameter which reduce the amount of inorganic salts and/or reagents. Green alternative for consuming of stoichiometric salts and reagents is to use a catalyst and this issue has been considered by pharmaceutical companies. However, demanding of the least expensive reagents has limited the applying of catalysts to be used widely.

Future perspective of green chemistry will be extended more seriously in many research areas. Product and environment should be considered together and it should be remembered

that this planet needs a balance of nature. Every attempt to heart this balance will come across more serious effects. That is why we need greener strategies and greener thinking. In this chapter, we have discussed the importance of solvents and catalysts for synthetic strategy at pharmaceutical chemistry. The progress and advantages about green solvents and bio- and organic-catalysts will be included in detail and we hope that whole of this knowledge will be a hand for both medicinal scientists and pharmaceutical industries.

2. Synthetic strategies with green solvents

In every product development processes and different industrial applications, solvents are needed in huge amounts resulting in abundant amounts of waste. Innovative technologies and different synthetic strategies have discussed solventless methods which are not accepted for all areas of research due to some market concerns. After the solventless ideas, chemists and medicinal scientists have searched out for solvents which suit green chemistry. According to Fischer, green solvent expresses the target to minimize the environmental impact coming from the consuming of solvents in chemical production [9]. Some strategies have emerged for solvents which can be mentioned as green. These are substitution of hazardous solvents resulting in more eco-friendly, biodegradable, and/or minimizing of ozone depletion potential, use of biosolvents (oleochemicals), and substitution of organic solvents which are supercritical fluids and ionic liquids [10].

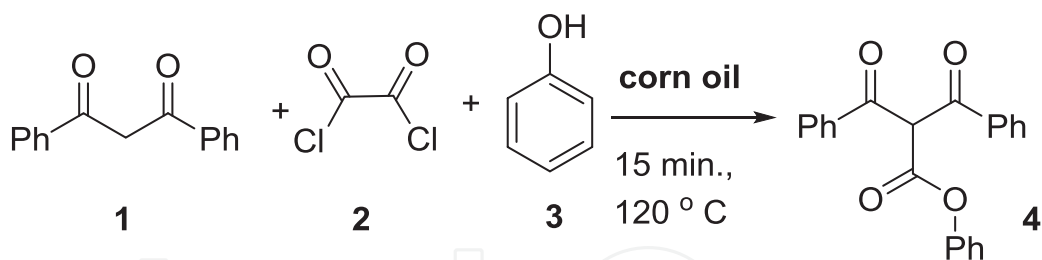
In the literature, many examples of green solvents can be seen for forming natural products, medicines, and important intermediate products which can be used for further synthesis.

2.1. Vegetable oils as a green solvent

Vegetable oils are oleochemicals which are extracted from many plants' seeds. They are renewable resources and have triglyceride structure in which three hydroxyl groups of glycerol are substituted with different fatty acids that make them liquids or solid products [11]. Vegetable oils are important food ingredient. Unfortunately, they have not considered as a green solvent so far except for a reaction which was published by us [12]. Vegetable oils have been utilized for biopolymers and might be evaluated by scientists who are looking for a new source of green solvent.

We have described the acylation and cyclization reaction that has been run in vegetable oil, especially corn oil. Utilization and advantages of vegetable oils have been discussed and yields, reaction times, and sustainability of vegetable oils have been compared both with each other and with toxic solvent, xylene. This reaction is the first example of vegetable oils and this idea should be concerned by more synthetic strategies due to the cost and efficacy of vegetable oils (**Scheme 1**) [12].

A mixture of dibenzoylmethane (**1**), oxalyl chloride (**2**), and phenol (**3**) was heated in corn oil at 120°C for 15 min. Authors have explained that CH₂ of compound **1** was acylated very easily.



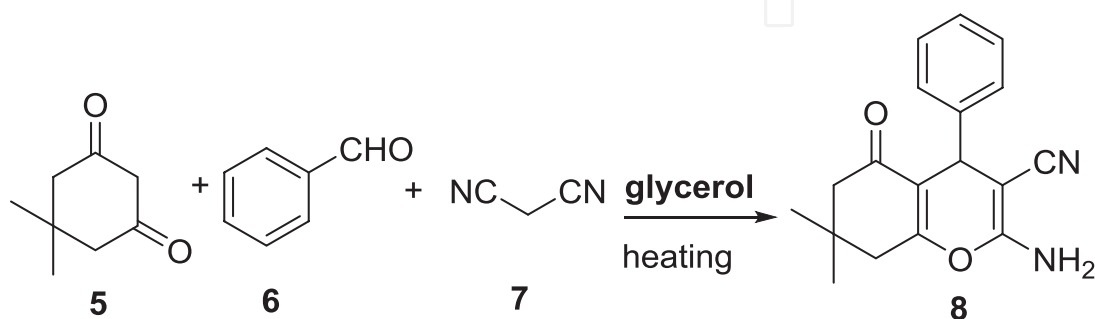
Scheme 1. Acylation reaction in corn oil [12].

2.2. Glycerol as a green solvent

Glycerol (also named as glycerin) is a polyalcohol and second part of oleochemicals which are derived from natural oils. Glycerol has been utilized in many different fields such as pharmaceutical and food industry, tobacco, and cellulose films [13]. Sustainability and low-cost of glycerol make it a good green solvent. With this respect, pharmaceutical companies and chemists have gotten more attention for glycerol as alternative to other organic solvents which are hazardous, volatile compounds, toxic, and harmful. Despite the fact that glycerol is a solvent and selected for many reactions, there are some obstacles which chemists and medical scientists have to overcome: (i) due to the viscosity of glycerol, it should be fluidified with a co-solvent. On the other hand, glycerol is much less viscous up to 60°C and reactions can be proceeded at temperatures higher than 60°C; (ii) glycerol might join the reaction as a reagent, as it has three OH groups which can be mentioned as acidic sites; (iii) glycerol has an enough length and donor atom in which it can obtain complexes with metal catalysts resulting in unwanted side products and/or unreactivity of catalysis. It can be said that there are two sides of glycerol and those can be mentioned for every solvents and reagents which are used in research areas. However, in here, we want to display advantages of glycerol in synthetic strategies.

Safaei et al. synthesized 4*H*-pyrans with catalyst-free, one-pot and three-component strategy using glycerol as green solvent (**Scheme 2**) [14]. Yield of reactions are high up to 93% and reactions gave many different types of pyran derivatives. Furthermore, authors have tested the reaction in water and they have seen that yield of the reactions was decreased down to 70%.

Cyclization reaction under atom economic and green solvent procedure is so important and this kind of reactions has prompted medicine scientists to reorganize the strategy for drug design.



Scheme 2. One-pot and three-component strategy in glycerol [14].

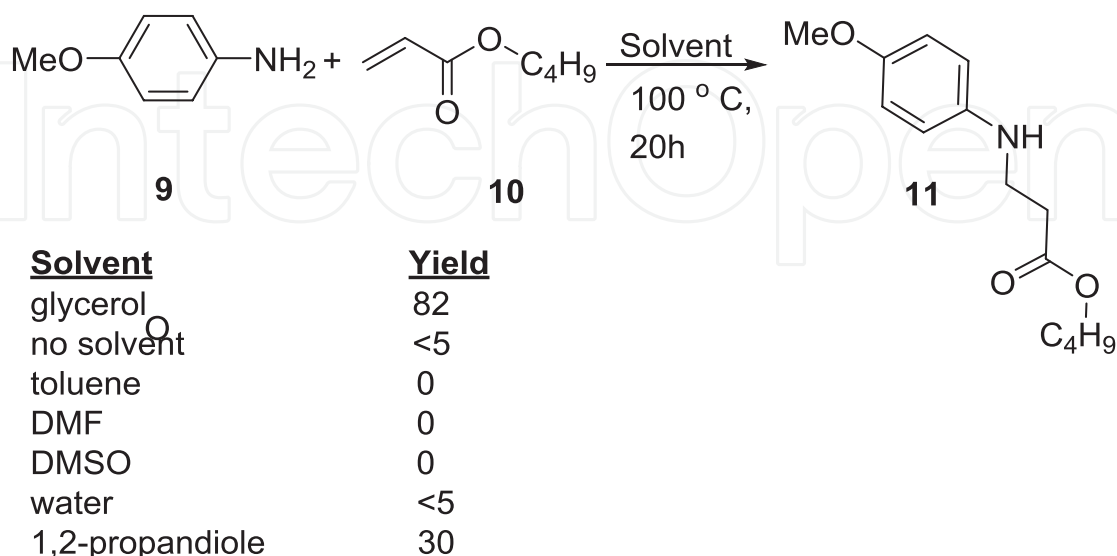
Jerome et al. have reported some common synthetic reactions on glycerol and they have discussed yield, reaction time, and sustainability of glycerol. One of the reactions that researchers have carried out was a nucleophilic attack on the β position of α,β -unsaturated carbonyl molecule. This type of reaction can be seen in many organic reactions and derivatization of lead compounds in pharmaceutical industries. The reaction showed that crude glycerol gave yield of the reaction up to 81% and reuse of glycerol as third time for same reactions did give the yield of the product perfectly (**Scheme 3**) [15].

Selectivity and green perspective of the reaction were evaluated by researchers. It is obvious that the reaction aforementioned was progressed in high yield on glycerol and the other organic solvents such as toluene, DMF, and DMSO did not produce any amount of expected product.

Glycerol is used for different reactions and demands on different application fields can be surpassed with modification of glycerol with simple thinking. This modification was done by Garcia et al. [16]. Garcia and his group have synthesized some alkylated derivatives of glycerol to be used as a solvent and evaluated their physical and chemical properties for further applications.

Organochalcogens are under investigation because of the importance of organochalcogen which includes one of an atom of Group 16 in the periodic table which are O, S, Se, and Te. Ebselen and its analogs are important molecules which show significant beneficial effects in primate model of neurodegenerative diseases (**Figure 1**) [17–19]. Organoselenium compound **12** is currently in clinical trials for cardiovascular indications [17]. The importance of these molecules has opened an area for the furnishing of these types of molecules.

With this respect, Leonardo et al. have described a green protocol without base and metal in glycerol for obtaining of organoselenium derivatives (**Scheme 4**) [19].



Scheme 3. Nucleophilic attack to the α,β -unsaturated carbonyl group in glycerol [15].

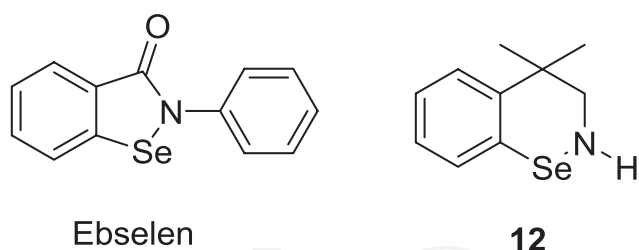
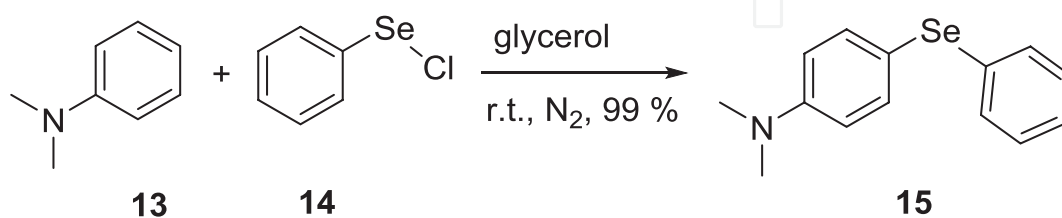


Figure 1. Two examples of organochalcogens.

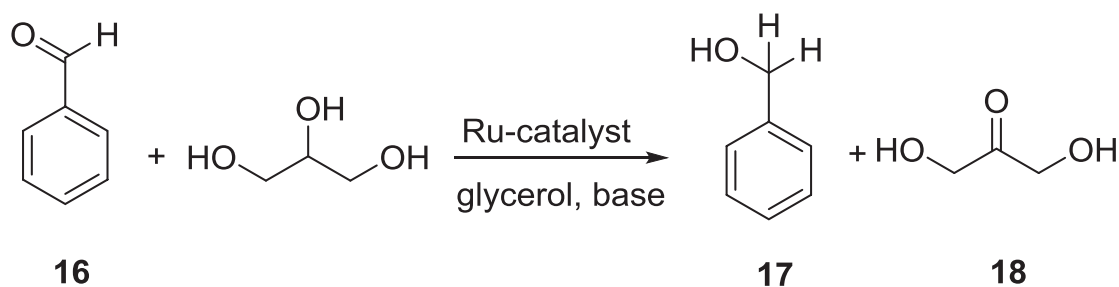


Scheme 4. Synthesis of organoselenium derivative in glycerol [19].

N,N-dimethylaniline (**13**) and haloselenium compound **14** was reacted in glycerol under an inert atmosphere to give organochalcogen molecule **15**. Waste product was HCl and yield of the reaction was excellent, 99%. Furthermore, the energy needed for running of the reaction was minimum, which was room temperature.

When scientists dig an unknown knowledge which has already existed, they have come across unexpected results. One of these situations was reported by Wolfson et al. One of the most important reactions is obviously hydrogenation of organic compounds in which catalysts and molecular hydrogen have been used. Wolfson et al. have achieved hydrogenation of benzaldehyde in glycerol which was used both solvent and hydrogen donor reagent using ruthenium catalyst (**Scheme 5**) [20].

This reaction represents a green protocol as glycerol has been used as both solvent and reagent resulting in atom economic strategy. It was seen that while glycerol oxidized to 1,3-dihydroxy-acetone (**18**), the reaction gave benzyl alcohol (**17**), one of the most important starting materials for organic reactions.



Scheme 5. Hydrogenation of benzaldehyde with catalyst and glycerol [20].

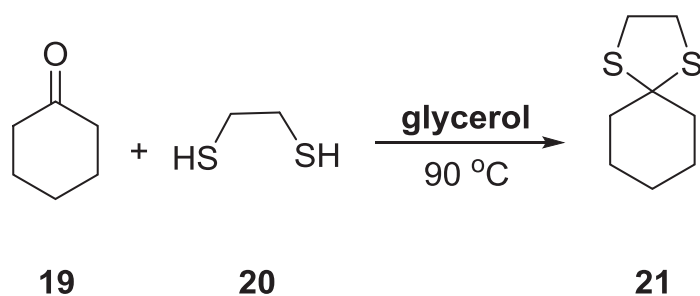
Wolfson et al. have reported the compatibility of glycerol in some named reactions such as nucleophilic substitution, reduction, catalytic reduction, Heck reaction, Asymmetric hydrogenation, and transesterification [21]. They have concluded that glycerol was successfully employed as versatile and alternative green solvent in a variety of organic reactions and synthetic methodologies. In addition, they have said that high products conversions and selectivities were achieved [21].

Functional group protection is still crucial in all fields of industries. Carbonyl protection can be progressed with a reaction between a molecule having a carbonyl group and 1,2- or 1,3-dithiole. Perin et al. have successfully applied a green protocol for protection of carbonyl group. Researchers have done the protection of ketones in glycerol (**Scheme 6**) [22]. Protection of carbonyl group of cyclohexanone (**19**) with 1,2-dithiole (**20**) was achieved in glycerol with good yield, 85% [22].

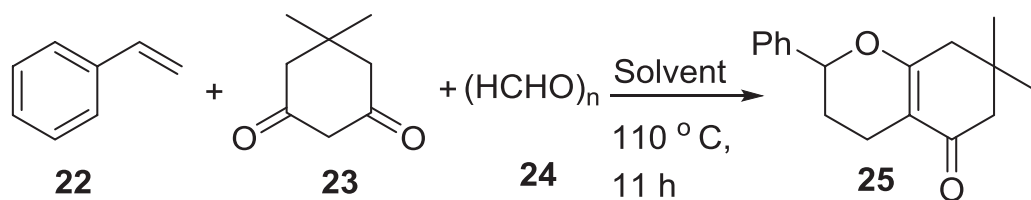
More recently, Gu et al. have described a cyclization reaction in glycerol in which a three-component strategy was utilized for pyran derivative **25** (**Scheme 7**) to occur [23]. Reactions were run with styrene (**22**), dimedone (**23**), and *p*-formaldehyde (**24**). The yield of the product was based on selected solvent and the most suitable solvent was selected as glycerol in which yield was seen as 68%. The other solvents showed less yield than glycerol. Furthermore, sustainability of glycerol was also tested and after three runs, yield was recorded to be found as 65%. An intermediate product of the reaction between dimedone and *p*-formaldehyde is formed and this intermediate product forms the pyrane ring by cyclizing with the styrene.

To furnish pyrazolo-pyran derivative **30**, Lu and his group have designed a reaction in which pyrazolone **28**, styrene analog **29**, and *p*-formaldehyde **24** were reacted in glycerol (**Scheme 8**) [24]. Reaction was progressed at 110°C and yield of the reaction was calculated as 78%. Same reaction in solvent-free and ionic liquids gave no product and was 48%, respectively. Pyrazolone derivative **28** was taken place by the reaction between phenyl hydrazine (**26**) and ethyl acetoacetate (**27**) through well-known condensation. Pyrazolone was not isolated and trapped with styrene analog **29** [24].

Glycerol and its etheric derivatives have been utilized both as a solvent and as a reagent for industrial processes and mg-scale synthetic reactions [25]. Unfortunately, glycerol is not still stood on the top of the industry due to some disadvantages such as viscosity, reactivity, and capability of being a ligand for metals. We hope that chemists and medical scientists will find



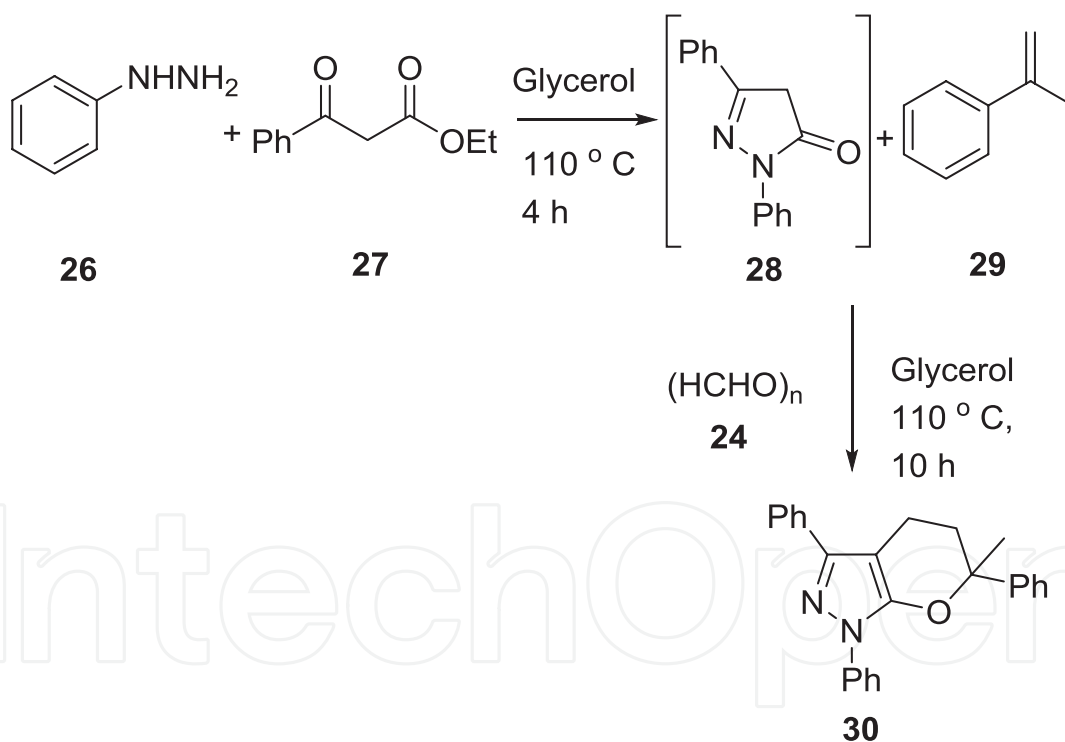
Scheme 6. Protection of carbonyl group with 1,2-dithiole in glycerol [22].



<u>Solvent</u>	<u>Yield</u>
H ₂ O	14
Toluene	< 10
No solvent	15
Glycerol	68
Reused in the third run	65

25

Scheme 7. Three-component strategy in glycerol in order to get pyrene derivative **25** [23].



Scheme 8. Synthesis of pyrazolo-pyrane in glycerol [24].

a way for greener alternative. Academicians have an important role in the ability for industry to implement green chemistry while industry can utilize the findings which are reactions, materials, and conditions with industrial relevance, to introduce more sustainable alternatives with lower risk and greener protocols for scale-up productivity.

2.3. Water as a green solvent

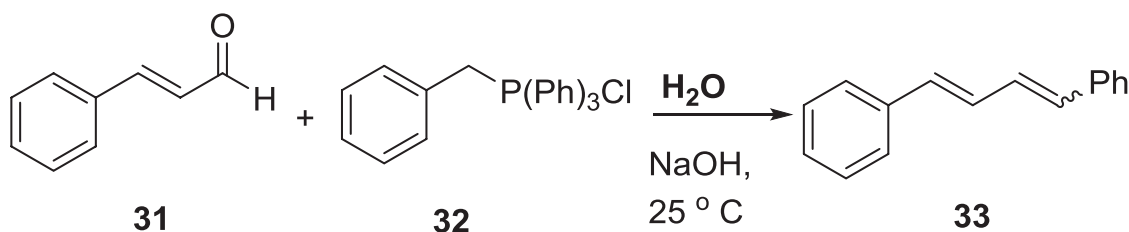
Water possesses many unique physical and chemical properties such as extensive hydrogen bonding, high heat capacity, large dielectric constant, and a large temperature window. Water as a solvent has therefore many advantages over conventional organic solvents. Furthermore, water can be selected as a green solvent due to cost, readily available, nontoxic, nonpolluting, and nonflammable. In fact, people do not call water as a chemical. In spite of many important advantages of water, it is still not commonly utilized as a sole solvent for synthetic strategies in research lab and industry as most of the organic compounds are not soluble in water. Nature selects water for its biological reactions and since a century, scientists have tried to mimic the synthetic reactions in water as occurred in nature. Scientists have been away from water for a long time because of an old doctrine in which old chemists say that the insoluble reagents do not yield any product. However, Sharpless has altered this old idea with a new thinking that reactions can be progressed “on” or “in” water means that solubility is not important for reactions [26]. Sharpless has described the reactions such as cycloaddition, Diels-Alder, nucleophilic opening of epoxide and Claisen rearrangement in which as the reactants were not soluble in water, the reactions were described as being on-water [26].

Basic reactions of organic chemistry are utilized in pharmaceutical chemistry to obtain medicines. One of these reactions is Wittig reaction. Wittig reaction is so important and it gives a new C–C bond. Morsch et al. have therefore reported a green protocol for Wittig reaction, run in water at 25°C (**Scheme 9**) [27].

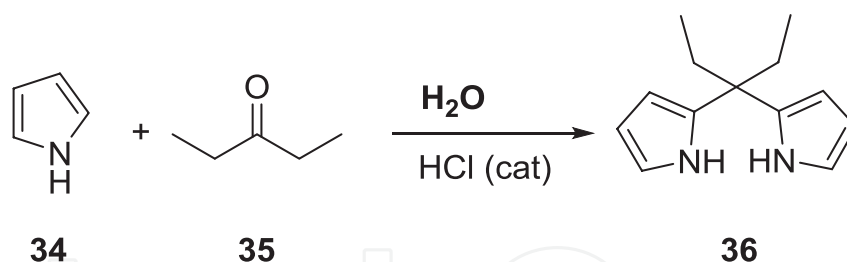
Pyrrole is one of the most critical starting materials for drug design and its reactions are also so important. For a green strategy, Sobral reported a reaction that pyrrole (**34**) and diethyl ketone (**35**) were reacted in water to get 2,2'-dipyrromethane (**36**) (**Scheme 10**) [28]. Sobral has reported that yield of the reaction was 80% and the reaction was progressed as gram-scaled [28].

Synthesis of isocoumarin in H₂O was reported by Xu et al. They have discussed that the reaction of salicylic acid (**37**) and alkyne **38** in the presence of ruthenium catalyst gave isocoumarin with yield of 85% (**Scheme 11**) [29].

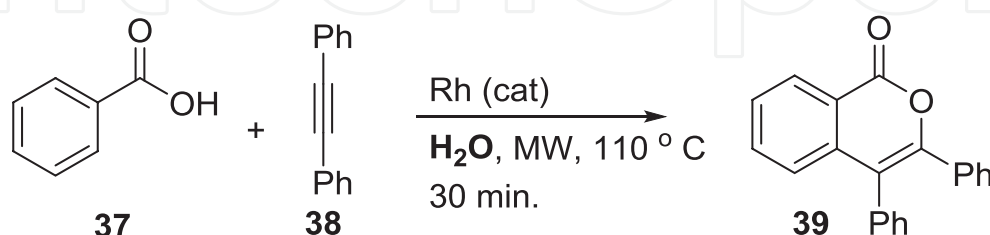
Pizzo and coworkers described the reaction of aza compound **40** and vinyl ether **41** resulting in pyridazine derivatives as a sole product with 92% for **42** and 6% for **43** and pyrrole derivative



Scheme 9. Wittig reaction in water [27].



Scheme 10. Dipyrromethane synthesis in water [28].

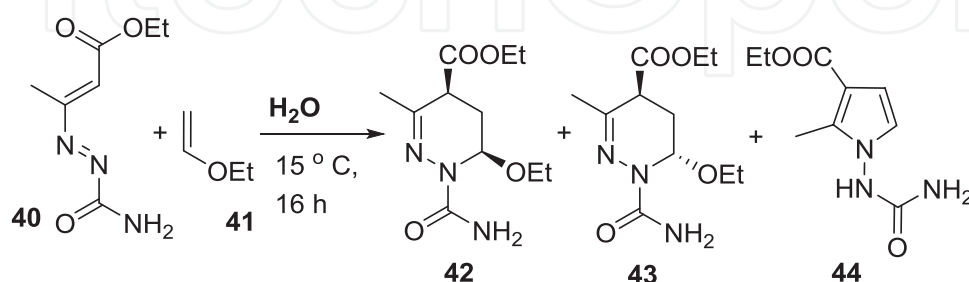


Scheme 11. Synthesis of isocoumarin in water [29].

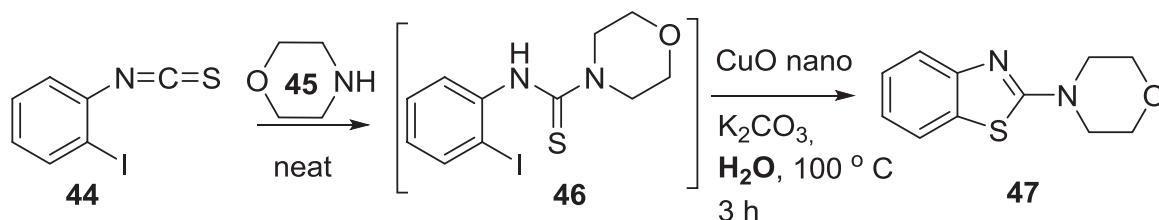
44 as a by-product with 2%. Authors reported that the reaction proceeded under heterogeneous medium because of poor solubility of aza compound **40** and vinyl ether **41** as called on-water reaction (**Scheme 12**) [30].

Synthesis of benzothiazole ring **47** was published by Patel and co-workers on water [31]. The reaction was started with iodo-benzo-isothiocyanate (**44**) and morpholine (**45**) to get thiourea derivative **46** which was not isolated. Thiourea derivative was cyclized with CuO-nanocatalyst using K_2CO_3 on water with yield of 92% (**Scheme 13**). They have also reported some points which were stereoselectivity, reusable catalyst, and no chromatographic purification because of high yields. They have also screened the effects of different solvents such as dioxane, DMF, and toluene which gave yields of 63, 70, and 55%, respectively [31].

Qu and his group studied the chromene derivative **49** in water. The reaction was named as highly green due to the fact that toxic solvent, catalyst, additive, and base were not used.



Scheme 12. Diels-Alder reaction of aza compound and vinyl ether "on-water" [30].



Scheme 13. On water reaction of benzothiazole [31].

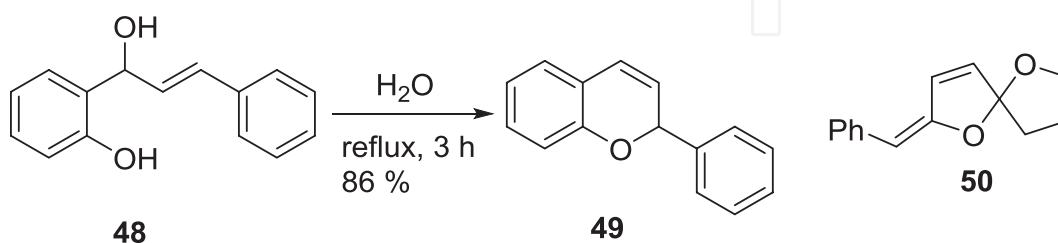
Yields of the reactions were varied between 74 and 95% [32]. They have synthesized spiroketal enol derivative **50** with the same strategy using furane ring, as well. Reactions were run in water with the addition of a small amount of hexafluoro-2-propanol (**Scheme 14**).

Lactam is an important ring as it is a part of antibiotic medicines such Cefaclor. With this respect, Pirrung and Sarma have reported the reaction in which acetoacetic acid (**51**), amine **53**, and isonitrile **52** were reacted in water (**Scheme 15**). The reaction was completed in 2 hours with yield of 93%. Authors have described that DCM gave the same result with less yield, 45% [33]. This reaction is a crucial example since it gives lactam in a water medium. Generally speaking, lactam ring is susceptible for ring opening toward nucleophile.

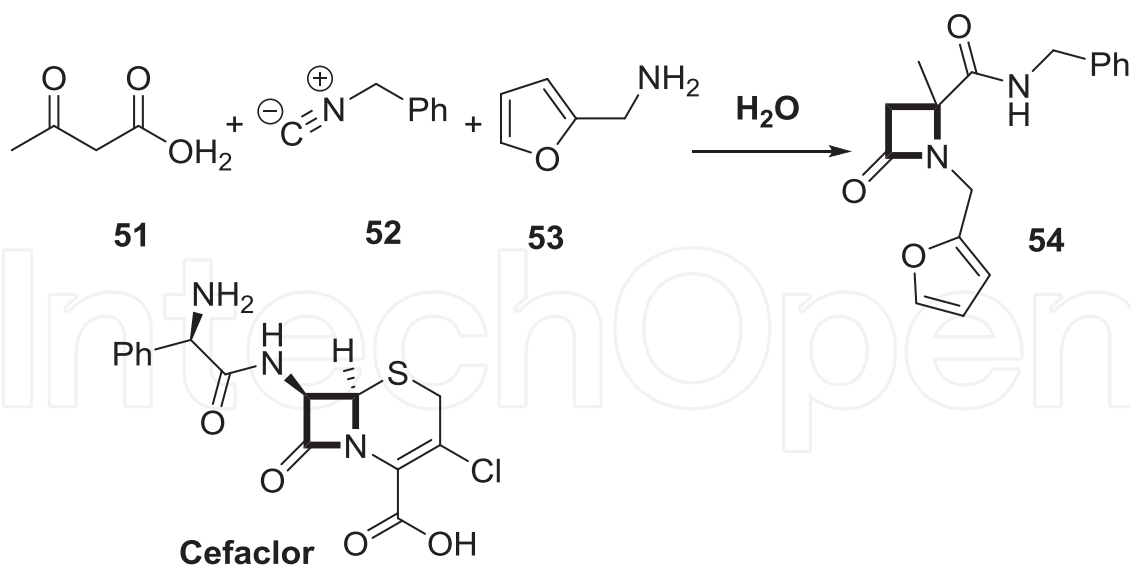
Besides lactam, a lactone is also so crucial ring which scientists want to synthesize. Lactone is presented in many natural and synthetic products which are used as a remedy for diseases. Fujimoto and coworkers studied the cyclization of allyl-iodoacetate using triethylborane in water (**Scheme 16**). Authors claimed that reaction progressed through radical and this is not a recently encountered result [34]. Compatibility of water was tested against some solvents. DMSO, DMF, MeCN, methanol, and benzene gave the cyclic product less than the reaction in water.

Wei and co-workers [35] reported that CH_2 of isatin was converted into oxime group (**Scheme 17**) which is a valuable synthetic building block, present in many bioactive molecules [36].

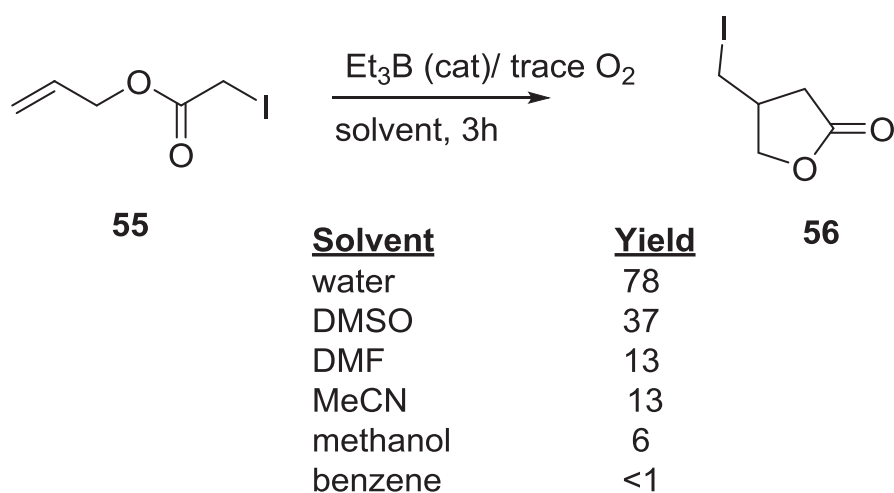
The reaction was experimented in both water and 1,4-dioxane, and yield of the reaction in water was 96% while the reaction in 1,4-dioxane was 5%. This derivatization was progressed through radical reaction and as said before, the radical reaction in water really challenges and thanks to scientists, these hard reactions have been achieved.



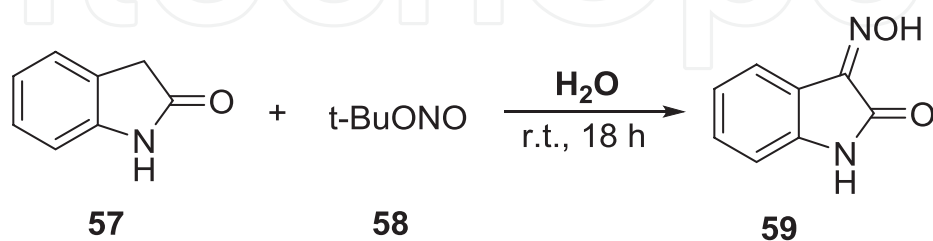
Scheme 14. Synthesize of chromene derivative in water [32].



Scheme 15. Synthesis of lactam ring in water [33].



Scheme 16. Yielding of lactone derivative [34].



Scheme 17. Conversion of isatin into oxime-isatin **59** [35].

Chen et al. have synthesized C-2 substituted indole derivatives **62** through a reaction in which aniline derivative **60** and organoboron salt **61** were used in water. For the acidity of the medium, tosyl acid was utilized and palladium acetate was consumed as a catalyst. This

reaction is one of the promising reactions those run in water. The reaction's yield was calculated as 92% and derivatization of indole was also studied (**Scheme 18**) [37].

Mishra and Verma have introduced a reaction for example of tetracyclic ring. Benzofuran derivative **63** and ortho-phenyldiamine (**64**) were reacted in water to get tetracyclic molecule with 88%. Solvent was tested for yield of the reaction and they have recorded that most of the proper solvents were water and the others were resulted in decreasing of the product down to 45%. Reaction was also studied using AgNO_3 and result of catalyzed reaction was unsatisfactory. They have optimized the reaction and explained that there was no need for catalyst, additive, and toxic solvent (**Scheme 19**) [38].

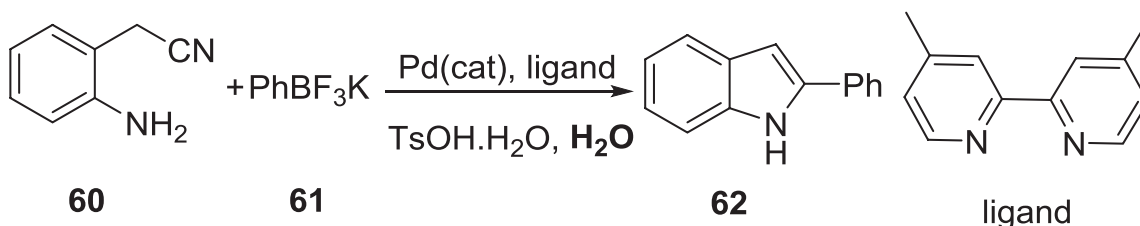
It is obvious that we can not mention all literature about green solvents, but we have desired to focus the most important literature. Exceptions for vegetable oil, glycerol and water have been considered more in detail in which we have given some important synthetic strategies. In next sub-section, we will share some examples of the other solvents which are pointed as green solvents such as ionic liquids, ethyl lactate, and so on.

2.4. The other solvents as mentioned in green chemistry

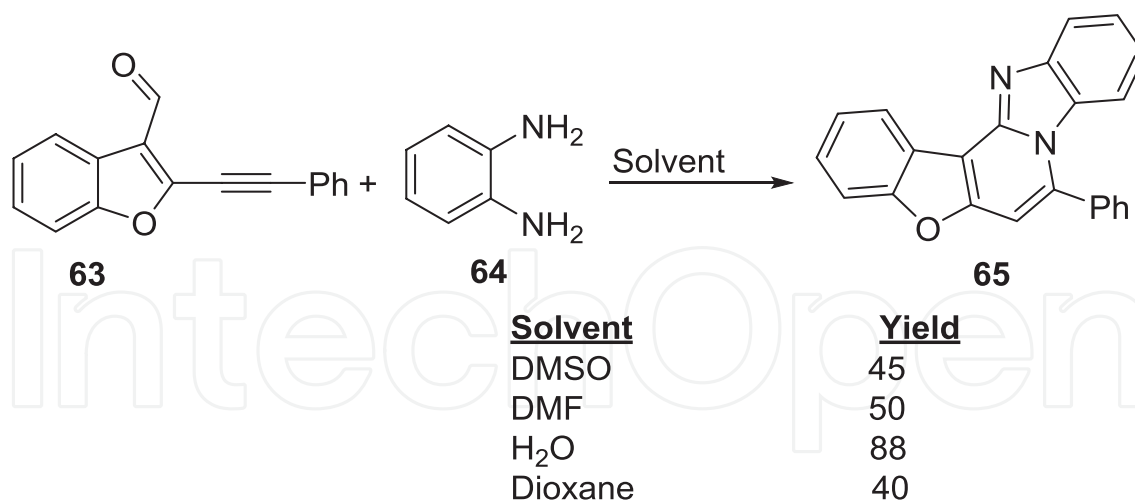
Ionic liquids are organic salts which are liquid at ambient temperatures. They are nonvolatile, nonflammable, thermally and chemically stable which make them as a better alternative for green chemistry than conventional organic solvents. Due to their high polarity, it can be used in many chemical and biochemical reactions. Besides special properties, they show less solubility in water and are generally immiscible with many organic solvents such hexane(s). They are much more viscous than other organic solvents which might be due to more hydrogen bonds and Van der Waals interactions. The most important feature of ionic liquids is that they can be tuned by changing cation, anion, and alkyl part, in which it is possible to obtain many manipulated green organic solvents [39]. Some common cation and anion parts are presented in **Figure 2**.

On the other hand, to tune the physical properties of ionic liquids, they have combined with hydrogen donor reagents such as glycerol (**68**), oxalic acid (**69**), and urea (**67**). This green alternative emerged because of the volatility of organic solvents. Ionic liquids are called deep eutectic solvents (DES) when composed by a quaternary ammonium salt and a hydrogen bond donor (**Figure 3**) [40]. There are some common combinations for DES which can be seen in **Figure 2**. They have been composed by different amounts of each part.

More recently, ethyl lactate **70** (**Figure 4**) was introduced as a potential green solvent to extract some natural ingredients from vegetable by Gan and co-workers [8].



Scheme 18. Synthesis of indole ring [37].



Scheme 19. Synthesis of tetracyclic molecule **65** in water [38].

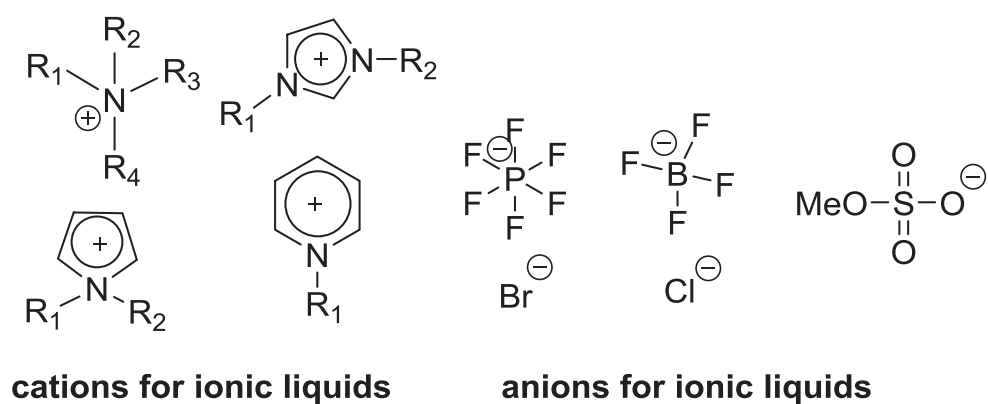


Figure 2. Cations and anions for ionic liquids.

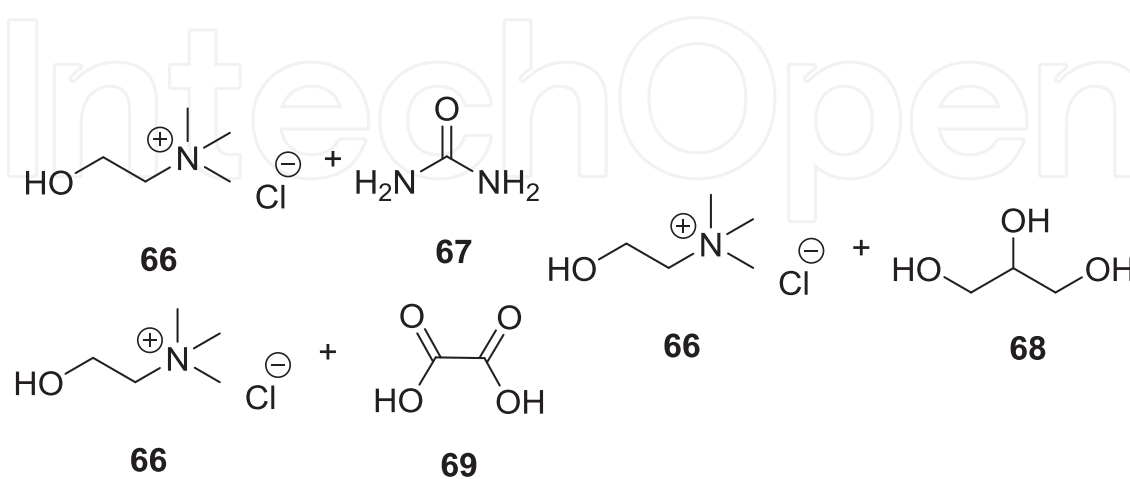


Figure 3. Some of the deep eutectic solvents.

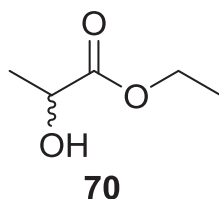


Figure 4. The structure of ethyl lactate.

They have studied ethyl lactate for green extraction and they have reported that understanding of its extraction capability and applicability should be improved. This solvent was experimented for plant extraction and might be tested in chemistry and pharmaceutical applications.

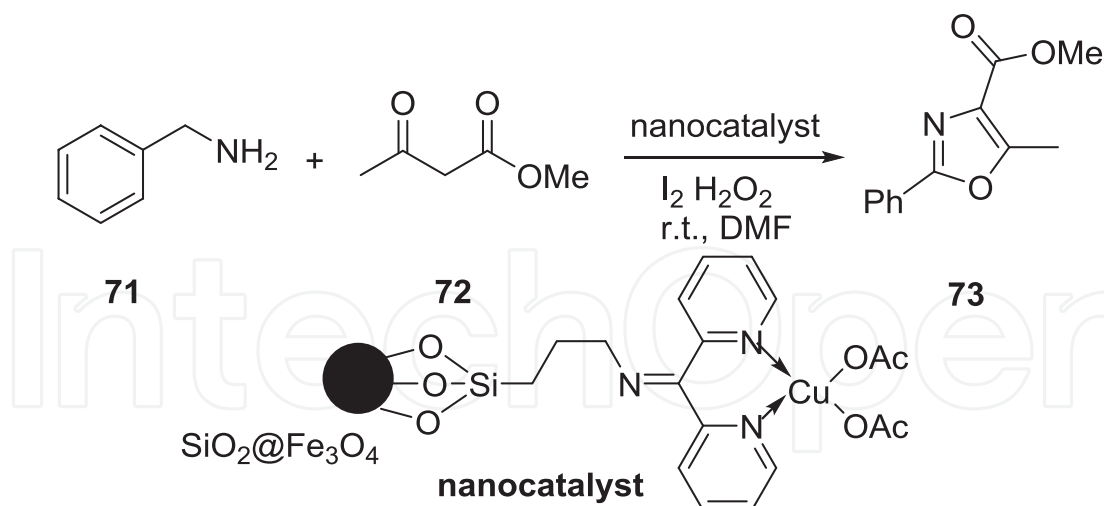
3. Synthetic strategies with catalysts

3.1. Nanocatalysts as a green solution

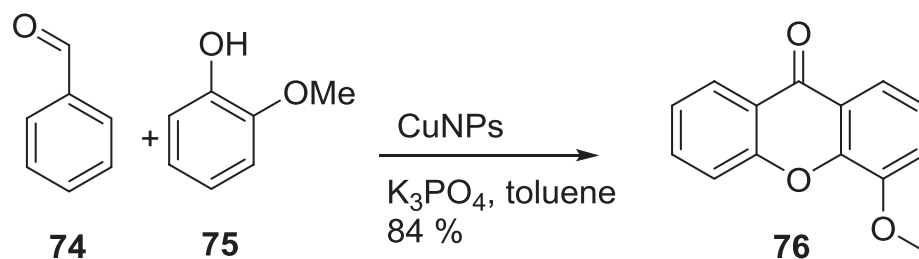
Catalyst is one of the rules of green chemistry and it should be considered by chemists and medical scientists [41]. There are two types of catalysts: heterogeneous and homogeneous. Homogeneous catalysts are more effective to obtain expected products than heterogeneous catalysts. However, isolation and reusable of homogeneous catalysts are the more problematic disadvantages when used for fine chemicals production in the chemical and pharmaceutical industry because of metal contamination of products. Less effective but more attractive heterogeneous catalysts are more favorable due to some of their advantages which are reusable and easier isolation from the medium. Besides heterogeneous catalyst, as a semi-heterogeneous catalyst, nanocatalysts have taken more attention as they have large surface-volume ratio resulting in more interactions between the surface of catalyst and reactant. However, there is still a contamination of catalyst even if it is filtered using specific filtration methods. More recently, thanks to magnetism, magnetic nanocatalysts have been obtained and extracted from medium with external magnetic field [42–46]. They have given more promising solution for chemical industries and it seems to be good candidates for active pharmaceutical ingredient (API) industry [42, 47].

Sharma et al. introduced a cyclization reaction using nanocatalyst [48]. They have obtained oxazole derivatives **73** with the reaction between benzyl amine (**71**) and methyl acetoacetate (**72**). Nanomagnetic catalyst was characterized by SEM, XRD, and FESEM. They have discussed that the yield of oxazole derivative decreased down to 5% absence of the nanocatalyst. Under reaction condition with nanocatalyst, conversion of the reaction was recorded as 100% which means that waste product is not produced (**Scheme 20**).

One-step synthesis of xanthenes was achieved by Gerbino and coworkers in which copper-based magnetically recoverable nanocatalyst was utilized [49]. Salicylaldehyde and phenol derivatives were reacted in toluene under ligand-free condition (**Scheme 21**). Reusable copper



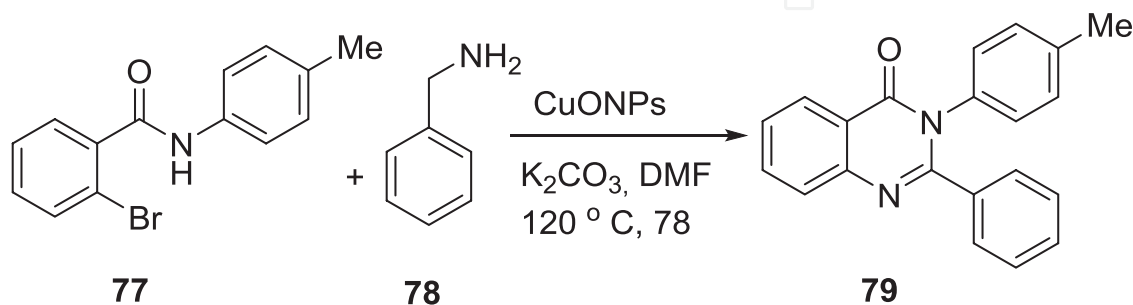
Scheme 20. Synthesis of oxazole derivatives on nanomagnetic catalyst [48].



Scheme 21. Furnishing of xanthone derivative **76** with copper-based nanocatalyst [49].

nanocatalyst was tested and was found to be 89% effective when used in fourth cycle. Altering of copper nanocatalyst with a conventional catalyst, CuCl or CuO, decreased the yield of the product down to 65 and 62%, respectively.

Quinazolinones **79** were formed with halo benzamide **77** and benzylamine using copper nanocatalyst (CuONPs) by Patel et al. (**Scheme 22**) [50]. Researchers showed that conventional copper catalysts such as CuBr, CuCl, and CuI have a less catalytic effect than copper nanocatalysts. Furthermore, without a catalyst, there is no cyclic product.



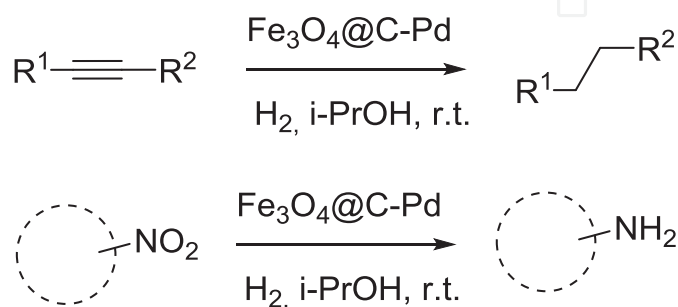
Scheme 22. Synthesis of quinazolinone ring [50].

Some of the most important synthetic strategies are named Suzuki, Heck, and Sonogashira reactions. These strategies give countless methods to chemists and medical scientists for further reactions in which fine chemicals and medicines can be obtained easily and in greener ways. More recently, these reactions have been progressed with magnetic nanocatalyst which are mentioned green strategies [51–56].

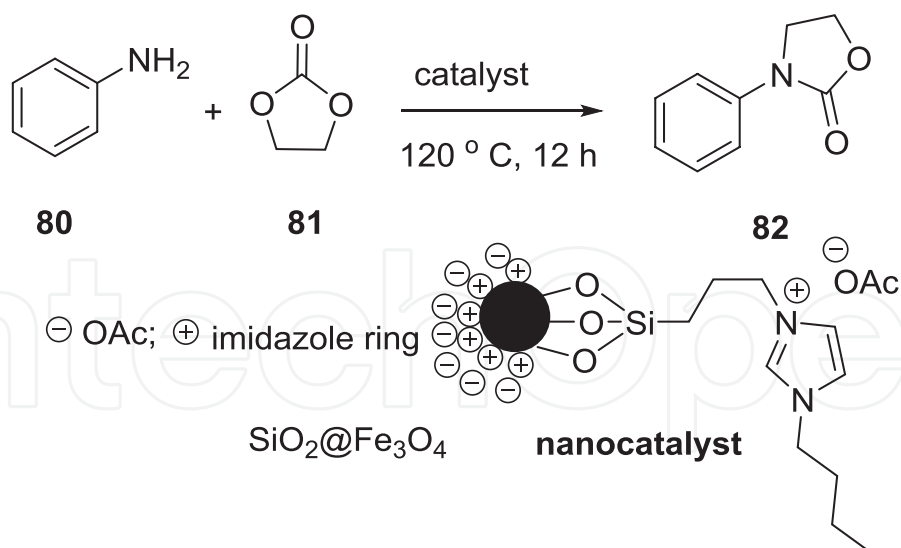
A green alternative for hydrogenation of π bonds and the nitro group was reported by Baig and Varma [57]. They have experimented lots of double and triple bonds, and nitro groups for reduction to obtain saturated alkyl unit and amine functional groups (**Scheme 23**). For fine chemicals, reduction is a critical reaction and thanks to this reaction, reduction can be done by a nanocatalyst which is magnetically active and can be removed easily with an external magnetic field from reaction medium [57].

N-aryl oxazolidine-2-ones framework **82** is an important ring which is a part of some clinically used medicines such as linezolid and Rivaroxaban which are sold as antibiotic and anticoagulant, respectively. In this spirit, forming of these rings with green chemistry would be very useful. Sharma's group has therefore studied on that strategy to obtain N-aryl-oxazolidine-2-ones using magnetic nanocatalyst (**Scheme 24**) [58]. They have tested nanocatalyst for reusability and seen that after eight runs, the yield of the product was recorded as 80–85% which was close to the first run, 95% [58]. Anilin (**80**) and ethylene carbonate (**81**) were reacted by means of nanocatalyst and the reaction gave almost quantitative yield. Removing of the nanocatalyst is so easy due to its magnetic feature. The nanocatalyst was made with iron (III) and iron (II) salts and the nano-iron oxide was reacted with silicone derivatives to obtain a silicon-coated nano-iron oxide. After then, imidazole-terminated silicon derivative was bonded to nano-iron oxide. Authors have assumed that nanocatalyst bonds to the oxygen atom of the carbonyl group of carbonate and makes therefore easy attack of aniline to a carbon atom of carbonate.

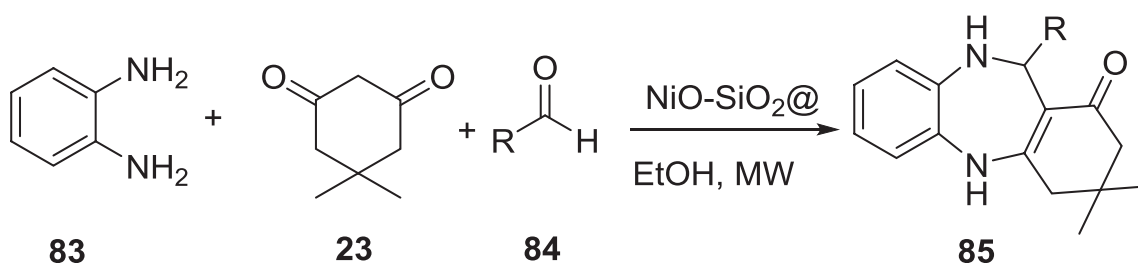
Benzodiazepine substructure is presented in some vital medicines such as diazepam, alprazolam, lorazepam, oxazepam, temazepam, and clonazepam. This structure can be obtained by many different methods [59, 60]. Beside presented methods, green chemistry is in progress to give diazepine derivatives. Lutfullah et al. have published an article in which they have displayed a green reaction using nanocatalyst to obtain tricyclic benzodiazepine derivatives **85** in good yields (**Scheme 25**). Nanocatalyst is silicon-coated nickel-oxide [61].



Scheme 23. Reduction reactions with magnetic nanocatalyst [57].



Scheme 24. N-aryl-oxazolidin-2-one with nanocatalyst [58].



Scheme 25. Synthesis of diazepine derivatives [61].

1,2-diamino benzene (**83**), dimedone (**23**), and aromatic aldehydes (**84**) were reacted in the reaction tube in which nanocatalyst was presented. All reactions were run in microwave synthesizer which is a good tool for green chemistry.

3.2. Biocatalysts as a green solution

In the literature, biocatalyst is a biological material which can be an isolated enzyme, a crude cell-free extract, an immobilized enzyme, or enzymes in whole microbial cells. Enzymes are critical endogens and have a vital role in living cells, which catalyze all the in vivo metabolic reactions to produce a necessary product for the body. To mimic the activity of enzymes for our reactions, since a century, enzymes have been utilized for the reactions in the laboratory. For many different purposes, scientists have used enzymes which are oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. These enzymes are utilized in the industry such as food, pharmacology, medicine, and textiles. Enzymes have unique properties which can sometimes not be mimicked by artificial organic products. Enzymes show highly stereoselectivity resulting in purely one isomer and can therefore decrease the cost of medicine because chirality has a high effect on the medicine cost when candidate medicine has more than one chiral center. This chemical potential forces the chemists and medical scientists to design biocatalysts to put them into the reaction flask [62, 63].

Biocatalysts are biodegradable, sustainable, reusable, more efficient, and more stereoselective which means more atom economic than conventional methods. With this respect, they are more powerful tools for green chemistry.

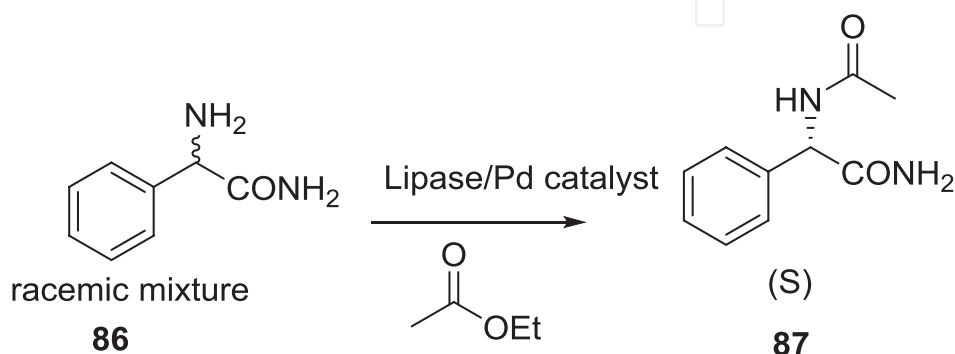
As mentioned before, chirality is one of the most critical criteria for pharmaceutical cost and pharmacologic effect of medicine which has a chiral center(s). It is well known that thalidomide tragedy revealed due to a racemic mixture of drug. Enzymes hence show up to solve this problem. Complete conversion of racemic amino acid amides to optically active amino acid derivatives was studied using lipase/Pd catalyst via dynamic kinetic resolution [64]. Authors have described that the reaction provided good yields (80–98%) and high enantiomeric excess (95–98% ee) (**Scheme 26**) [64].

Savile and co-workers have reported an efficient biocatalytic process to replace a recently implemented Rh-catalyzed asymmetric enamine hydrogenation for antidiabetic compound sitagliptin. Current synthesis of sitagliptin involves enamine formation followed by asymmetric hydrogenation at high pressure using Rh-based chiral catalyst in which sitagliptin was formed in 97% ee with trace amount of Rh [65]. Savile's synthetic route showed green reaction that is direct amination of prositagliptin ketone **88** to furnish enantiopure sitagliptin **89** (99.95% ee) followed by phosphate salt formation to get sitagliptin phosphate **90** (**Scheme 27**) [65].

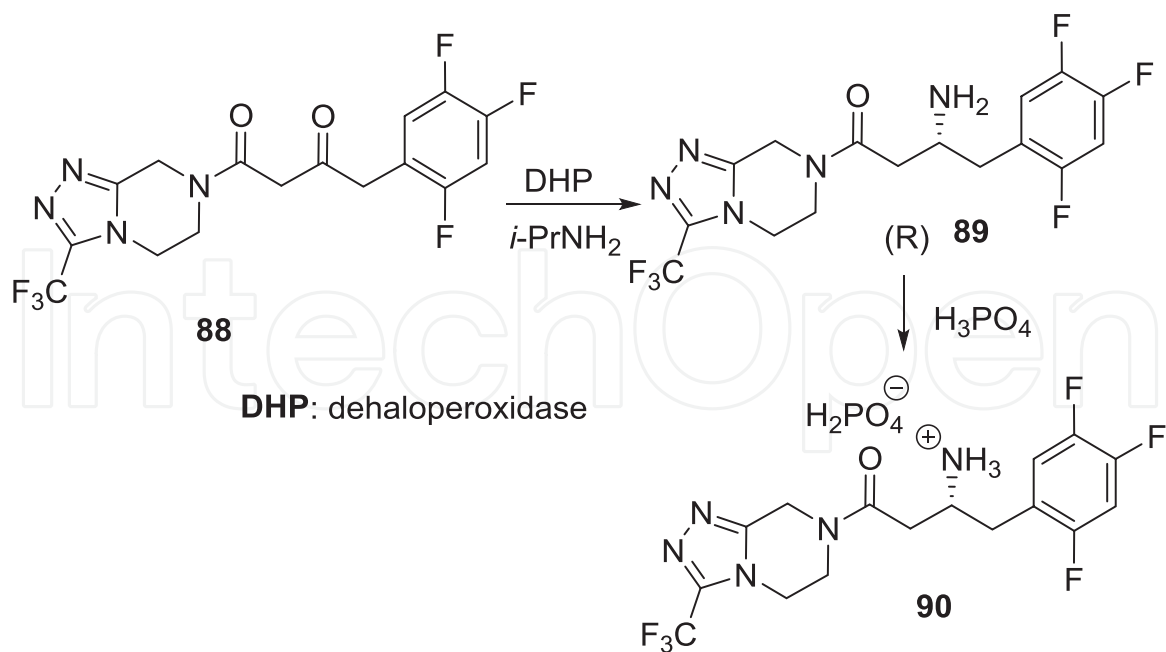
Ghiladi et al. have emerged a biocatalytic green process for the oxidation of pyrrole ring to provide pyrroline-2-one (**92**) [66]. Dehaloperoxidase (DHP) was supplied for biocatalytic reaction and for oxygen source, hydrogen peroxide was consumed. Finally, pyrroline-2-one was obtained with 31.7% conversion (**Scheme 28**). Authors explained that some derivatives of pyrrole were oxidized up to 100% conversion.

Chen and co-workers experimented to improve the performance of immobilized lipase by interfacial activation on iron-oxide nanoparticles. They have tested immobilized enzyme stability and displayed that immobilized lipase exhibited much better stabilities [67]. Furthermore, with iron-oxide nanoparticles, the enzyme was removed easily as mentioned in magnetic nanocatalyst.

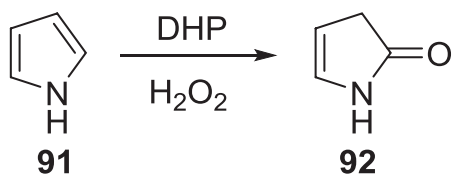
Besides iron oxide nanoparticles, enzyme immobilization on carbon nanotubes (CNTs) and graphene is applied for many chemical reactions such as cyclization, selective amination, trans esterification, and redox reactions and biosensing applications for detection of glucose, phenol, and hydrogen peroxide [62, 63].



Scheme 26. Resolution of racemic amino acid amides by lipase/Pd [64].

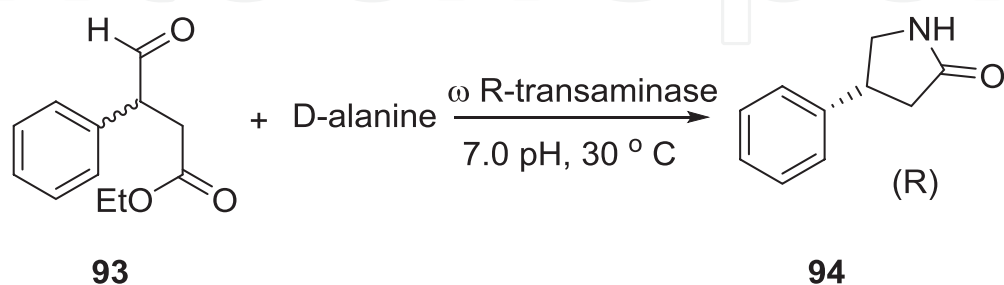


Scheme 27. Synthesis of sitagliptin phosphate with green chemistry.



Scheme 28. Oxidation of pyrrole by DHP.

Kroutil et al. reported the formation of lactam ring **94** starting from 4-oxo ester **93** in which lactate dehydrogenase, transaminase, and D-alanine were added to the reaction medium. The reaction was progressed at 30°C and 7.0 pH. Reaction was finalized to obtaining lactam derivative with 92% yield (**Scheme 29**) [68].



Scheme 29. Cyclization of keto-ester to lactam by enzyme.

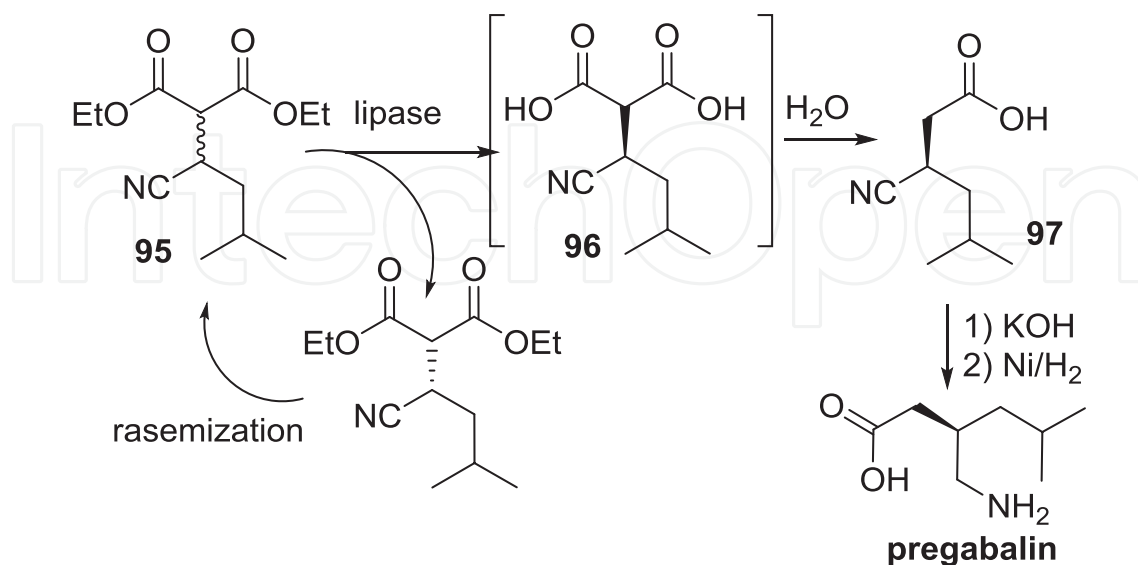
4. Case studies in green chemistry

In 2002, Pfizer won the U.S. Presidential Green Chemistry Award for alternative synthetic pathways for its innovative manufacturing process for sertraline hydrochloride which is the active ingredient of Zoloft that is used to treat clinical depression. Furthermore, pregabalin, sold as Lyrica, is manufactured by Pfizer for the management of neuropathic pain and epilepsy. Pfizer has designed a green route for the synthesis of pregabalin and they have reported that almost 38 million liters of alcoholic organic solvents and nearly 2000 metrics tons of raw materials were eliminated on an annual basis. Their achievements were based on biocatalyst, lipase, which was used for resolution of cyano diester **95** (**Scheme 30**) [69].

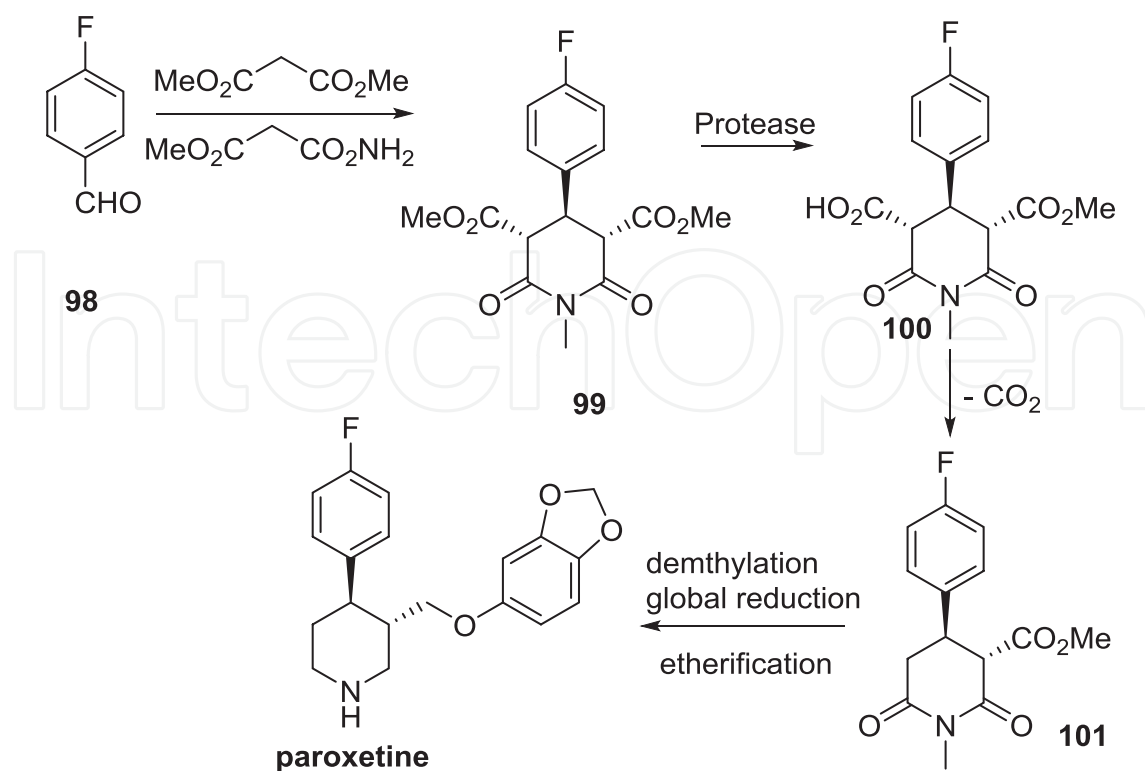
GlaxoSmithKline company has announced a green reaction way for paroxetine, sold Seroxat, and Paxil, which is used for anxiety disorder. They have discussed that the yield of the overall transformation was almost double that of the process in conventional route, resulting in a greener, shorter, and more cost-efficient way. Critical step was applying of protease enzyme which was regioselectively hydrolyzed an ester group (**Scheme 31**) [69].

Sertraline hydrochloride as known Zoloft is a selective inhibitor of serotonin reuptake which is utilized for the curing of depression [70]. When it was synthesized by conventional synthetic route, chemical reagents and metal salts were consumed. On the other hand, removing of metal salts and Pd/C catalyst gave more selective and greener protocol (**Scheme 32**) [71].

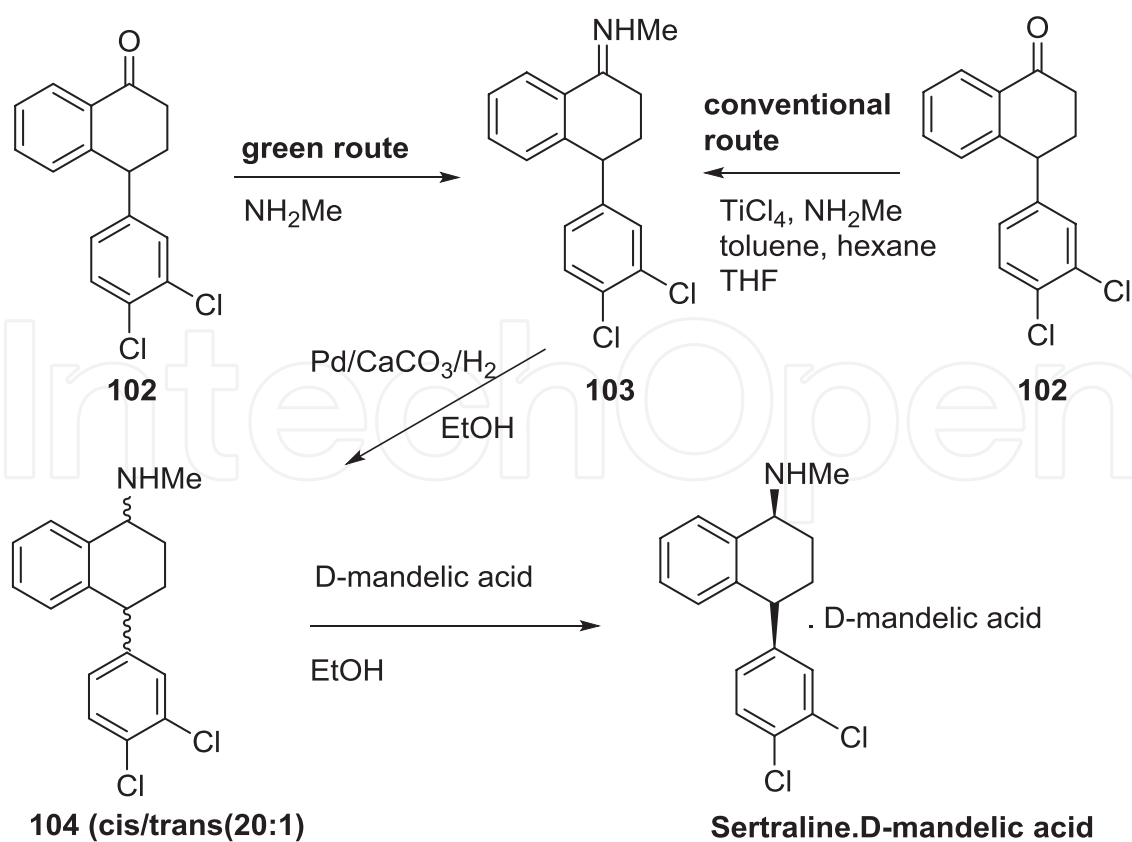
Colberg and co-workers in Pfizer Global Research and Development have designed a green protocol for sertraline in which toxic solvents such as toluene, hexane were removed from



Scheme 30. Green protocol for pregabalin.



Scheme 31. Formation of paroxetine through biocatalytic route.



Scheme 32. Green protocol for sertraline [71].

the strategy and comparison of solvent utilization between the first commercial route and the new green route showed that 76.000 L solvents, 440 tons/year of $\text{TiO}_2\text{-MeNH}_2\text{.HCl}$ waste and about 40 tons of the unwanted trans isomer waste were eliminated [71].

5. Conclusion

Green chemistry is getting extended in many researches and industry areas. The reason is that the resources of the world are limited and it is necessary to be consumed with caution. On the other hand, we have already witnessed that researchers and pharmaceutical companies searched out for green protocol when manufactured the pharmaceuticals. In this spirit, most pharmaceutical companies are making increasing efforts to limit waste and avoid air and water pollution. Green solvents, nanocatalysts, and biocatalysts give many opportunities for greener methods in which impact on the environment and the cost of pharmaceuticals can be decreased. We hope that this chapter and the others give a brief consideration of importance of green chemistry. With advantages of green chemistry, hopefully, industry will alter conventional methods with greener ones.

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